RESPONSE

I. Status of the Claims

Prior to the fourth Action, claims 1-68 and 102-117 were pending and have been examined. Presently, claims 14, 15, 17, 18, 106 and 108 have been amended without prejudice. No claims have been canceled. Claims 118-132 have been added, which are unified with the examined claims and fully supported by the specification as filed.

Claims 1-68 and 102-132 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Allowed and Allowable Claims in the Fourth Action

In the first Action, claims 1-47 and 49-68, *i.e.*, all but one pending claim, were indicated as allowed or allowable. In the second Action, many of the previously allowed and allowable claims were rejected; claims 54-65 were allowed and claims 14-16, 26-34, 38 and 39 were indicated as allowable. In the third and fourth Actions, new art was cited and more of the previously allowed and allowable claims were rejected.

Presently, claims 48 and 54-65 have been allowed (fourth Action at summary page). Although the fourth Action at page 5 later characterizes claims 48 and 54-65 as "allowable", as claims 48 and 54 are independent claims, each of claims 48 and 54-65 are allowed, as indicated at the summary page. Each of claims 13-18 are also allowable, but "objected to" as being dependent on a rejected base claim (fourth Action at summary page; page 5).

The present response overcomes the new rejections and places all claims in condition for allowance. Nonetheless, Applicants have also focused on the allowed and allowable claims from the fourth Action and the current claim set includes several claims that the Examiner has most recently indicated to be patentable.

III. Support for the Claims

Support for the amended and new claims exists in the pending claims, and also throughout the original specification as filed. Although additional fees should not be required for the new claims, any small entity fees deemed necessary for their introduction should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4100.002000.

Allowable claims 14, 15, 17 and 18 have been amended to depend directly from allowed claim 48.

Claims 106 and 108 have also been amended to depend indirectly from allowed claim 48.

New dependent claims 118-130 are based upon pending claims 19, 20, 21, 25, 26, 27, 28, 29, 30, 31, 35, 36, 37, 38 and 39, and are supported thereby.

New claim 131 is based upon claim 1 with two revisions. Firstly, the composition is clarified as a "structural matrix-nucleic acid composition", which is supported throughout the specification, with literal written description support at least at page 4, line 27 to page 5, line 13, for example. Secondly, the structural matrix-nucleic acid composition is substantially free from residues of organic solvents. This is a more positive recitation of certain inherent features of the invention, which is supported throughout the specification, with particular support at least at page 31, lines 17-18.

New claim 132 is also based upon claim 1 with three revisions, the first being the same grammatical change referring to the "structural matrix-nucleic acid composition" as set forth above. The second and third changes are to emphasize that the nucleic acid is a "bioactive nucleic acid" that is "expressed" in a cell upon contact of the structural matrix-nucleic acid composition with a cell. This is also a more positive recitation of inherent features of the invention, which are supported throughout the specification, with exemplary support at least in the specification at least at page 33, line 26 and in original claims 21, 22, 26-29 and 73-101.

It will therefore be understood that no new matter is included within any of the amended or new claims.

IV. Rejection of Claims 1-12, 19-47, 49-53, 66-68 and 102-117 Under 35 U.S.C. § 103(a)

The only rejection in the case is that of claims 1-12, 19-47, 49-53, 66-68 and 102-117 under 35 U.S.C. § 103(a) as allegedly being legally obvious over Mikos *et al.*, U.S. Patent No. 5,514,378 ("Mikos"), Grinstaff *et al.*, U.S. Patent No. 5,639,473 ("Grinstaff") and Mineau-Hanschke, U.S. Patent No. 5,965,125 ("Mineau-Hanschke") in combination. Although Applicants respectfully traverse, the rejection is overcome.

A. Claims Allowed in the Fourth Action

Claims 48 and 54-65 are allowed in the fourth Action and claims 13-18 are indicated as allowable, but "objected to". Applicants respectfully traverse the rejection as applied to the remaining claims, which is addressed and overcome below. Nonetheless, Applicants have placed claims 13-18, 106 and 108 in condition for allowance by depending on claim 48. New claims 118-130 also depend on claim 48 and are therefore in condition for allowance.

B. The Rejection is Overcome

Despite the previous allowance, claims 1-12, 19-47, 49-53, 66-68 and 102-117 are newly rejected as allegedly being obvious over Mikos, Grinstaff and Mineau-Hanschke, in combination. Applicants respectfully traverse.

Mikos is cited as concerning a biocompatible porous membrane structure comprising one of a particular group of synthetic polymers (fourth Action at page 3). The Action admits that Mikos does not teach or suggest the incorporation of a nucleic acid segment, a central component of the presently claimed invention.

The Action then combines Mikos with two other references, without establishing a proper combination, and summarily concludes that the invention is unpatentable. Indeed, the Action

even states that the claimed invention is "clearly anticipated" (fourth Action bridging pages 4 and 5), whereas the rejection of record is one of alleged obviousness over three references in combination. Should the Office intend an anticipation rejection, such a rejection would have to be made as part of a non-Final Office Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references. MPEP 706.07(d).

The Mikos methods to prepare porous membrane structures involve the use of organic solvents and high temperatures. Where Mikos concerns three-dimensional structures, these are simply prepared by laminating the membranes together (fourth Action at page 3, Mikos throughout, *e.g.*, abstract).

As detailed in the present specification, the use of organic solvents teaches away from the incorporation of nucleic acids. The specification explains that residues of organic solvents, which remain in polymers after processing techniques such as described in Mikos, damage transplanted cells and nearby tissue and/or inactivate biologically active factors incorporated into the polymer matrix for controlled release. High temperatures also denature any biologically active molecules incorporated into the matrix (specification from page 3, line 26 to page 4, line 2).

The structural matrices of the claimed invention are prepared from a fabrication process that involves a gas foaming/particulate leaching (GF-PL) technique that does not use organic solvents or high temperatures (specification throughout, *e.g.*, page 31, lines 17-18). This is an important component of the claimed invention not taught or suggested in Mikos.

In embodiments of the present invention where nucleic acids are first incorporated into microspheres, which are then used to form structural matrices (*e.g.*, claims 44, 52 and 53), the structural matrices are still processed using the gas foaming technique recited in the claims. The

gas foaming acts to remove any residual solvent that may result from the microsphere processing, without introducing any new solvents or other adverse processing conditions.

The use of organic solvents in Mikos thus teaches away from the present invention, which is strong evidence of patentability. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531-1532 (Fed. Cir. 1988). Moreover, as the use of organic solvents is incompatible with the incorporation of bioactive nucleic acids, this renders Mikos unsatisfactory for the intended purpose, and there can be no suggestion or motivation towards the claimed invention. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Mikos' use of organic solvents also renders improper the proposed combination of Mikos with Grinstaff. This is important as mention of nucleic acids exists only in Grinstaff, the Action agreeing that Mikos "does not teach or suggest the incorporation of a nucleic acid segment into the structural matrix" (fourth Action at page 3, emphasis added).

Before the P.T.O. may combine the disclosure of two or more prior art references in order to establish a *prima facie* case of obviousness, there must be some teaching, suggestion or motivation to combine the references. *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). In the present case, there is no teaching, suggestion or motivation to combine Mikos with Grinstaff and Mineau-Hanschke, particularly as Mikos' use of organic solvents is inconsistent with nucleic acids. Accordingly, the rejection is *prima facie* improper and should be withdrawn.

Even if Mikos is combined with Grinstaff and Mineau-Hanschke, the rejection is still improper. Mikos fails to teach or suggest the claimed invention (fourth Action at page 3), and in fact teaches away from the invention, and Grinstaff and Mineau-Hanschke do not cure the deficiencies of the primary reference.

Grinstaff is cited as concerning a biocompatible polymer composition for *in vivo* gene delivery comprising a nucleic acid construct (fourth Action at page 3). The compositions of

Grinstaff are limited to polymeric shells (Grinstaff throughout) associated with "biologics", preferably a polymeric shell of disulfide-crosslinked protein microspheres containing nucleic acids (Grinstaff throughout, *e.g.*, claim 1, column 6, Example 13).

The present invention requires a "structural matrix". The structural matrix-nucleic acid compositions of the invention have 3-dimensional matrices with controlled porosity that facilitate migration and proliferation of cells and nucleic acid transfection (specification at pages 4 and 5). The polymeric shells of Grinstaff are not, in any way, a "structural matrix" as required by the claimed invention. Grinstaff has thus been improperly combined with Mikos and, even if combined, Mikos and Grinstaff fail to teach or suggest the structural matrix-nucleic acid compositions of the claimed invention.

The polymeric shells and microparticles of Grinstaff deliver biologics "for parenteral administration in aqueous suspension" (Grinstaff at column 6, lines 8-16). The microparticles of Grinstaff, like the microcapsules of Wheatley (earlier cited and withdrawn), thus concern the *passive release* of biological substances. This is the opposite of the claimed invention, which provides "structural matrix" nucleic acid compositions *into which cells migrate, encounter and take up the nucleic acids and express the encoded products* (specification at pages 7, 8, 15, 25, 26, 38, 41, 56, 69, 76, 77, 78, 79, 81, 82 and 114).

Grinstaff does not teach or suggest compositions of "structural matrices" and nucleic acids as in the present invention, in which cells penetrate or grow into the structural matrices, contact and take up the nucleic acids and express the encoded products, but concerns only polymeric shells for passive release of biological substances. Therefore, not only does Grinstaff fail to teach or suggest the present invention, Grinstaff teaches away from the claimed invention, which is evidence of patentability. *In re Dow Chemical Co., supra.*

The stated rejection is based on Mikos, Grinstaff and Mineau-Hanschke in combination (fourth Action at page 3). Mineau-Hanschke is discussed in the Action at pages 3 and 4. However, the Action then summarizes the rejection as allegedly being obvious to "modify the porous matrix of Mikos by incorporating nucleic acid sequences as taught by Grinstaff" (fourth Action at page 4). Thus, there seems to be no role for Mineau-Hanschke in the rejection, which renders the rejection *prima facie* improper.

Mineau-Hanschke is described as concerning a hybrid matrix composition comprising insoluble collagen fibrils and a plurality of genetically engineered cells embedded in the matrix (fourth Action at page 3). Mineau-Hanschke actually concerns a hybrid matrix of insoluble collagen fibrils, a plurality of genetically engineered cells and a plurality of microcapsules to improve the function of the collagen matrix (Mineau-Hanschke throughout, *e.g.*, abstract, claim 1, column 1, lines 57-59).

Even if Mineau-Hanschke is combined with Mikos and Grinstaff, the rejection is still improper. Mikos and Grinstaff, both alone and in combination, fail to teach or suggest the claimed invention. Mineau-Hanschke not only fails to cure the deficiencies of Mikos and Grinstaff, but further teaches away from the claimed invention in important respects.

Mineau-Hanschke is limited to hybrid matrices comprising collagen and microcapsules designed to improve the function of the collagen matrix. Mineau-Hanschke therefore has no relevance to matrices other than collagen matrices, such as matrices of synthetic polymers or alginates.

Importantly, the collagen-microcapsule matrices of Mineau-Hanschke do not contain nucleic acid segments other than in the context of the genetically engineered cells. Thus, while Mineau-Hanschke concerns pre-formed engineered cells for transplantation, it does not teach or

suggest transfecting cells with nucleic acids. This significant difference serves to highlight further surprising and important features of this invention over Mineau-Hanschke.

The matrix-nucleic acid compositions of the present invention provide a structural matrix into which cells migrate, encounter and take up the nucleic acids and express the encoded products. The controlled porosity and other physical properties of the structural matrices allow for improved control over cellular migration, transfection and proliferation, thus allowing the number and type of cell populations that are exposed to the nucleic acids to be regulated (specification throughout, *e.g.*, pages 4-5 and page 7, lines 25-27).

Rather than providing structural matrices into which cells penetrate or grow, contact and take up the nucleic acids therein and express the encoded products, as in the present invention, Mineau-Hanschke resorts to genetically engineering cells *ex vivo*. The genetically engineered cells, which must be capable of attaching to collagen and/or the microspheres (Mineau-Hanschke at column 3, lines 10-11), are then provided to an animal in the hybrid matrix of insoluble collagen fibrils and microcapsules.

Thus, Mineau-Hanschke teaches away from the claimed invention by requiring the exogenous preparation of individual engineered cells, which are then administered in the hybrid matrix. As detailed in the specification, methods such as described in Mineau-Hanschke are limited by the need to isolate and expand cells *in vitro* and by poor survival of many cell types following transplantation (specification at page 29, lines 12-13).

The present invention, in contrast, provides structural matrix-nucleic acid compositions that create and maintain a space for cellular transfection to occur, allow the exposure of cells to genetic material for extended periods of time and control the numbers and populations of cells exposed to the nucleic acids (specification at page 31). In addition to the sustained provision of genetic material and the transfection of large numbers of cells *in vivo*, the structural matrix-

nucleic acid compositions of the invention are able to transfect cells distant from the administration site (specification at page 31, lines 8-11, emphasis added), which is not possible in Mineau-Hanschke.

The specification teaches that the matrix-bioactive nucleic acid compositions of the present invention provide spatial and temporal control of nucleic acid release and bioavailability, and can thus be used in the treatment of a wide variety of disorders and injuries that occur in a number of tissues. The working examples include the sustained release, cellular uptake and expression of nucleic acids to significantly enhance granulation tissue deposition and blood vessel growth in developing tissues (specification at Example XVII). This evidently requires the coordinated actions of various cell types, not the limited provision of a particular engineered cell, as in Mineau-Hanschke.

In summary, and in contrast to the Action's position at pages 4 and 5, Mikos, Grinstaff and Mineau-Hanschke, either alone or in combination, do not teach or suggest the claimed invention. As the technique used throughout the present invention produces a unique product, and as the processing steps are recited in the claims, the claimed compositions[1] are distinguished over the prior art of record.

Not only is "the structure implied by the steps" recited in the claims distinguishable over the cited prior art of record (Action at page 5), the techniques of the primary reference are incompatible with the preparation of structural matrices comprising nucleic acids, as the prior art processing techniques would damage, inactivate and/or denature the nucleic acids. Although all claims are novel and non-obvious over the cited art, claims 21-35, 41-46, 104, 113, 116, 131 and 132 particularly highlight operable features of the invention, which could not be achieved by the

[1]The Action's statement that "the composition as claimed merely reads upon a porous gel containing a nucleic acid segment" (Action bridging pages 4 and 5) is not a correct summary of claim 1 or the claimed invention as a whole.

processing conditions of the cited art and are thus even further distanced from the combination of art of record.

In light of the foregoing, the § 103(a) rejection is overcome and all claims are in condition for allowance.

V. PTO Form 1449s

Copies of certain timely-submitted PTO Form 1449s initialed by the Examiner have still not been provided, despite Applicants' earlier requests. In particular, initialed PTO Form 1449s listing references A35, C25-C37 and C49-C50 have not been provided to the Applicants. For the convenience of the Office, Applicants enclose additional copies of these PTO Form 1449s and respectfully request that a copy be included in the Notice of Allowance, or in the next communication from the Office.

VI. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the claims already allowed and the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Kaushal have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
Williams, Morgan & Amerson, P.C.
Customer No. 23720

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicants

10333 Richmond, Suite 1100
Houston, Texas, 77042
(713) 934-4079
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